CT Radiogenomic Characterization of the Alternative Lengthening of Telomeres Phenotype in Pancreatic Neuroendocrine Tumors

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OBJECTIVE. The objective of this study was to identify imaging characteristics in patients with known pancreatic neuroendocrine tumors (PanNETs) that predict the alternative lengthening of telomeres (ALT) phenotype by blinded retrospective review of preoperative multiphasic CT scans.

MATERIALS AND METHODS. For this retrospective study of 121 preoperative CT examinations of patients with resected PanNETs, two radiologists independently reviewed the CT examinations for tumor characteristics including size, shape, cystic or necrotic elements, calcifications, invasion of adjacent organs and vessels, biliary duct dilatation, pancreatic duct dilatation, and hepatic metastases. Univariate analysis of association of CT characteristics with ALT phenotype was performed with Fisher exact tests or *t* tests, and multivariate analysis was assessed by multiple logistic regression.

RESULTS. Univariate analysis showed that the following CT features were significantly associated with the ALT phenotype: lobulated or irregular tumor shape ($p = 0.001$), tumor necrosis ($p = 0.002$), vascular invasion ($p < 0.001$), pancreatic duct dilatation ($p < 0.001$), and hepatic metastasis ($p < 0.001$). Multivariate analysis found that the combination of pancreatic duct dilatation, hepatic metastasis, and size of tumor ≥ 3 cm was a strong predictor of ALT phenotype (odds ratio = 20.3; 95% CI = 2.3–176.3; AUC = 0.58; $p = 0.006$).

CONCLUSION. This study showed that several preoperative CT features of PanNETs are associated with the ALT phenotype, which is known to predict poor prognosis. Additionally, CT findings of intratumoral calcifications and metastases predicted poor survival independent of the ALT status.

Keywords: alternative lengthening of telomeres (ALT), ATRX, CT, DAXX, neuroendocrine tumor, pancreas, pancreatic neuroendocrine tumor, radiomics

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Although pancreatic neuroendocrine tumors (PanNETs) are relatively uncommon, representing only 1.3% of newly diagnosed malignant pancreatic neoplasms [1], their incidence has increased approximately fivefold over the past 40 years, likely owing in large part to advances in medical imaging [2]. Because 85% of PanNETs are nonfunctioning and do not present with a classic syndrome of hormonal hyperexcretion [3], approximately 40% of these tumors are diagnosed incidentally [4], frequently at CT. Multiphasic contrast-enhanced CT (CECT) typically shows a hyperenhancing pancreatic parenchymal mass best visualized in the arterial phase [5, 6] with a diagnostic sensitivity and specificity of 73% and 96%, respectively [7]. Because of the broad range of tumor behavior, ranging from relatively indolent to metastatic, determination of clinical prognosis is challenging. However, recent discoveries regarding the molecular genetics underlying the pathogenesis of PanNETs have yielded several new markers that show a promising ability to predict tumor behavior.

The genes *DAXX* (death domain-associated protein) and *ATRX* (α-thalassemia/mental retardation X-linked) encode subunits of a protein complex involved in histone modification of pericentric and telomeric chromatin [8] and are mutated in 43% of PanNETs [9]. Altered expression of either of these genes by mutation or epigenetic silencing is highly associated with the alternative lengthening of telomeres (ALT) pathway, which is believed to be a key step in PanNET oncogenesis [10]. PanNETs with the ALT phenotype and DAXX or ATRX deficiency are strongly associated with aggressive tumor behavior including metastasis and higher tumor stage, resulting in decreased survival; however, some studies suggest better survival in the subset of patients with metastases [9–12].

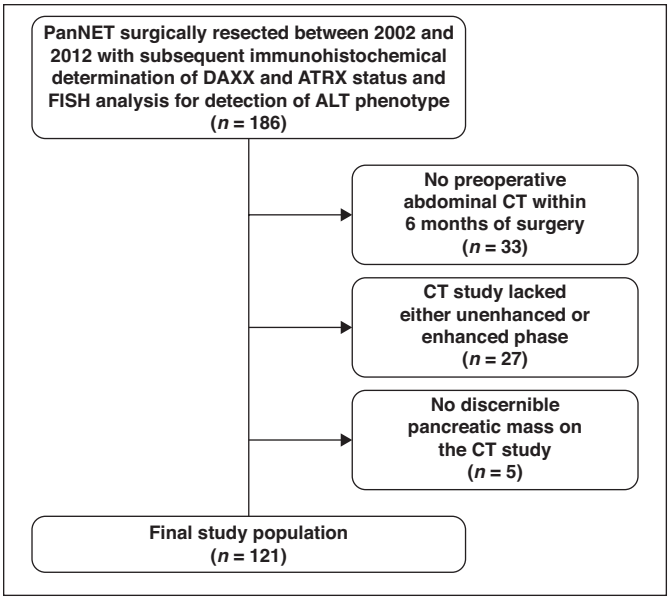


Fig. 1—Flowchart depicts process for identification of study population. Inclusion criteria were preoperative multiphasic abdominal CT within 6 months of surgical resection of pancreatic neuroendocrine tumor (PanNET). Exclusion criteria were absence of identifiable discrete pancreatic mass on CT and CT study lacked either unenhanced or enhanced phase. ALT = alternative lengthening of telomeres, DAXX = death domain-associated protein, ATRX = α-thalassemia/mental retardation X-linked), FISH = fluorescence in situ hybridization.

Patients with ALT-positive PanNETs have a 40% 5-year disease-free survival (DFS) and 50% 10-year disease-specific survival (DSS), compared with 96% DFS and 89% DSS for patients with ALT-negative PanNETs [13].

We hypothesized that a set of tumor features that distinguish ALT-positive from ALT-negative PanNETs could be identified from preoperative CT scans, which could potentially provide valuable preoperative data regarding tumor behavior and prognosis. The objective of this study was to investigate the CT features of PanNETs associated with the ALT-positive phenotype.

Materials and Methods

Institutional review board approval was obtained, and the requirement for informed consent was waived for this retrospective study. HIPAA compliance was maintained throughout all phases of the study.

Study Population

Review of pathology reports between 2002 and 2012 identified 186 patients who underwent resection of a PanNET with subsequent identification of ALT phenotype by fluorescence in situ hybridization (FISH). The PACS at University of Pittsburgh Medical Center was queried for each patient and identified 121 multiphasic abdominal CT examinations performed within 6 months of surgery that showed a pancreatic mass, as summarized in Figure 1. The median time between multiphasic CT and surgery was 32 days (range, 28.7–83.2 days). The study population (median age at the time of preoperative CT, 59.5 years) was composed of 68 men (median age, 59.5 years; range, 31.2–83.1 years) and 53 women (median age, 60.0 years; range, 28.7–82.5 years). Clinical and follow-up data were obtained from patient paper and electronic medical records. Length of follow-up and disease-related (i.e., PanNET) mortality were recorded.

Fluorescence In Situ Hybridization Determination of Alternative Lengthening of Telomeres Phenotype

The presence or absence of the ALT phenotype in surgically resected PanNETs was determined by FISH, with methods previously described by Singhi et al. [13]. The ALT phenotype was detected in 32 of 121 tumors (26%).

Imaging Technique

Of the 121 CT studies included in our study, 111 were performed within our institution's hospital network using a pancreatic mass protocol. This protocol includes an unenhanced phase, pancreatic parenchymal phase, and portal venous phase acquired at thickness intervals of 0.625 mm and reconstructed into 2.5-mm slices, after the oral administration of 16 oz (0.5 L) of water and nonionic, low-osmolar IV iodinated contrast material. Patients were injected with a weight-based dosage (range, 70–150 mL) of nonionic contrast medium including iopamidol with an iodine concentration of 370 mg/mL (Isovue 370, Bracco Diagnostics; $n = 64$), ioversol with an iodine concentration of 350 mg/mL (Optiray 350, Guerbet; $n = 46$), iohexol with an iodine concentration of 300 mg/mL (Omnipaque 300, GE Healthcare; $n = 3$), or iopromide with an iodine concentration of 300 mg I/mL (Ultravist 300, Bayer HealthCare; $n = 1$). The contrast agent was not documented in the remaining seven studies. Images are acquired from the diaphragm to the iliac crest in the unenhanced phase and then during the pancreatic parenchymal and portal venous phases. By using bolus-tracking methods (SmartPrep, GE Healthcare), pancreatic parenchymal phase scanning was initiated 20 seconds after enhancement of the abdominal aorta reached 100 HU. Portal venous phase scanning was performed at a fixed scan delay of 70 seconds.

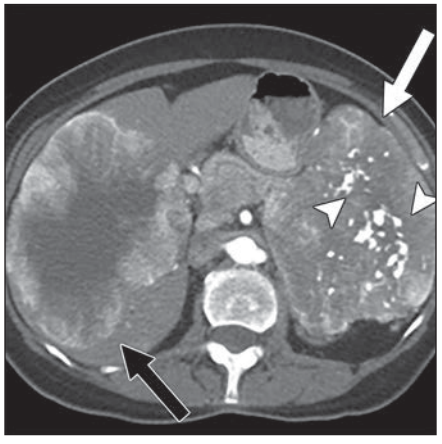


Fig. 2—58-year-old woman with alternative lengthening of telomeres (ALT)-positive pancreatic neuroendocrine tumor. Arterial phase contrast-enhanced CT image shows large, necrotic, irregularly shaped mass arising from pancreatic tail (*white arrow*) with numerous intratumoral calcifications (*arrowheads*). Large necrotic metastasis has replaced much of right hepatic lobe (*black arrow*).

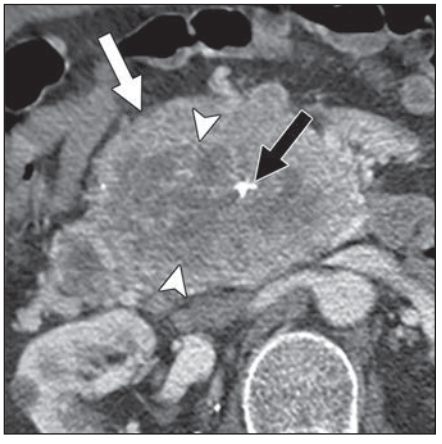


Fig. 3—48-year-old man with alternative lengthening of telomeres (ALT)-positive pancreatic neuroendocrine tumor. Arterial phase contrast-enhanced CT image shows enhancing mass (*white arrow*) with central necrosis (*arrowheads*) and calcification (*black arrow*) arising from pancreatic head.

Fig. 4—48-year-old man with alternative lengthening of telomeres (ALT)-positive pancreatic neuroendocrine tumor. Arterial phase contrast-enhanced CT image shows heterogeneously enhancing mass (*arrow*) arising from pancreatic neck, resulting in obstruction and dilatation of main pancreatic duct to diameter of 2.5 cm (*arrowheads*).

Fig. 5—78-year-old man with alternative lengthening of telomeres (ALT)-negative pancreatic neuroendocrine tumor. Arterial phase contrast-enhanced CT image shows rim-enhancing round cystic mass (*arrow*) in pancreatic tail without upstream pancreatic duct dilation.

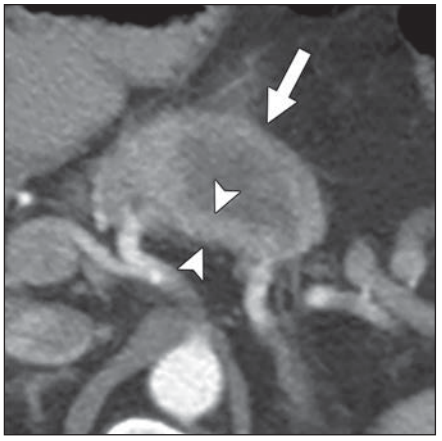


Fig. 6—40-year-old man with alternative lengthening of telomeres (ALT)-positive pancreatic neuroendocrine tumor. Arterial phase contrast-enhanced CT image shows centrally necrotic enhancing mass arising from pancreatic body (*arrow*) and encasing splenic artery (*arrowheads*).

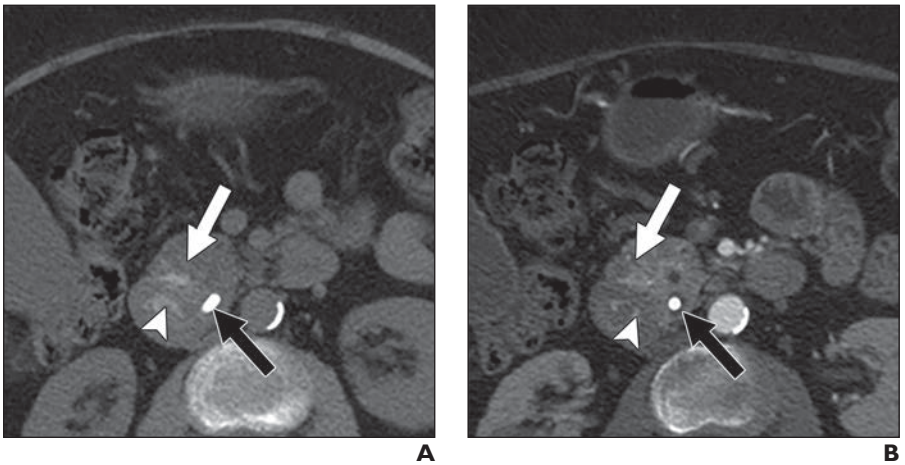
The remaining 10 multiphasic CECT examinations were performed at outside institutions, and the DICOM files were uploaded to the PACS. Each of these 10 studies was a triphasic examination that included unenhanced, arterial, and portal venous phase images of the abdomen.

Image Analysis

Two fellowship-trained abdominal imaging radiologists with 10 and 3 years of experience interpreted the abdominal CT images independently. Although both radiologists were aware that each patient included in the study had undergone surgical resection of a pathology-proven PanNET, they were blinded to ALT phenotype during the process of image analysis.

For each CT study, the number of discrete pancreatic tumors was recorded. For patients with multiple lesions, the largest lesion was considered to be the index tumor for the purpose of this analysis. Size (in millimeters) was determined by measuring the greatest dimension in the axial plane. Net tumor enhancement was determined by placing a circular or ovoid ROI within a representative enhancing portion the tumor on both the pancreatic parenchymal phase and portal venous phase series to identify the maximum attenuation (in Hounsfield units) in either phase of enhancement and by subtracting the attenuation measurement of the same location on the unenhanced phase series. One patient had a tumor with a very thin enhancing rim with central cystic change, and a reliable measurement of CT attenuation of the enhancing rim could not be obtained. This patient was, therefore, excluded from the contrast enhancement analysis.

The following qualitative data were recorded: the location of the index tumor (head, neck, body, or tail of the pancreas) (Figs. 2 and 3), shape of the index tumor (round, ovoid, lobulated, or irregular) (Figs. 2 and 4), presence or absence of cystic components (nonenhancing areas with water attenuation) (Fig. 5), presence or absence of tumor necrosis (nonenhancing areas with attenuation greater than water) (Figs. 2 and 6), presence or absence of intratumoral calcifications, invasion of adjacent organs (Fig. 7), encasement or invasion of vessels (specifically the superior mesenteric artery and vein, splenic artery and vein, common hepatic artery, celiac axis, and main portal vein) (Fig. 6), pancreatic duct dilatation (defined as ≥ 3 mm in diameter) (Fig. 4), biliary duct dilatation (defined as ≥ 7 mm in diameter), and hepatic metastases (Fig. 2). Vascular encasement or invasion was defined as 180° or greater of contact with a vessel by the tumor or occlusion of the vessel. For the purposes of analysis, vascular involvement was dichotomized into no encasement or in-



A **B**

Fig. 7—70-year-old woman with alternative lengthening of telomeres (ALT)-negative pancreatic neuroendocrine tumor.
A and **B,** Unenhanced (**A**) and arterial phase contrast-enhanced (**B**) CT images show ill-defined heterogeneously enhancing infiltrative mass with indistinct margins in pancreatic head (*white arrow*). Mass contains calcifications and infiltrates wall of second portion of duodenum (*arrowhead*) and ampulla, which is causing biliary duct obstruction. Note plastic stent in common bile duct (*black arrow*).

TABLE 1: Patient Demographic Characteristics and Number of Pancreatic Neuroendocrine Tumors (PanNETs) per Patient by Alternative Lengthening of Telomeres (ALT) Phenotype

Variable	ALT-Positive (*n* = 32)	ALT-Negative (*n* = 89)	*p*
Sex			
Male	17 (53.1)	51 (57.3)	
Female	15 (46.9)	38 (42.7)	
Age at CT (y), median	60.1	59.2	0.667[a]
No. of PanNETs			0.455[b]
1 PanNET	31 (96.9)	80 (89.9)	
2 PanNETs	1 (3.1)	8 (9.0)	
> 2 PanNETs	0 (0)	1 (1.1)	

Note—Data are number (%) of patients unless indicated otherwise.
[a]Two-tailed *t* test.
[b]Chi-square test.

vasion (defined as < 180° of contact of a vessel by the tumor) and encasement or invasion. Similarly, the location of the index tumor was grouped into two categories: head or neck and body or tail. Tumor shape was grouped either as round or ovoid or as lobulated or irregular.

After the two radiologists completed their independent review of all 121 CT studies, their interpretations were compared and discordances were noted. CT studies for which discordant findings were identified were reviewed collaboratively by both radiologists, and a final interpretation was reached by consensus.

Statistical Analysis

Univariate analysis included two-tailed *t* tests to assess differences in quantitative variables (tumor size and net enhancement) and chi-square or Fisher exact tests to assess for differences in qualitative variables between ALT-positive and ALT-negative groups. Multiple logistic regression with stepwise selection of variables was used to generate a statistical model to predict ALT-positive phenotype. Multivariate analysis of CT features of PanNETs predictive of survival was performed by Cox proportional hazards regression model. Statistical analyses were performed using SAS (version 9.4, SAS Institute) and SPSS Statistics (version 25.0, IBM) for Macintosh (Apple), with $p < 0.05$ considered as the threshold for statistical significance for all tests.

Results

Patient Demographics

Patient demographic characteristics are summarized in Table 1. CT showed a single PanNET tumor in 111 patients (91.7%), two PanNETs in nine (7.4%) patients, and seven PanNETs in a single patient (0.8%).

Univariate Analysis

Results of the univariate analysis are presented in Table 2. ALT-positive tumors were significantly larger than ALT-negative tumors, measuring 53 and 28 mm (mean), respectively ($p < 0.001$). The following CT features were significantly associated with the ALT-positive phenotype: lobulated or irregular tumor shape ($p = 0.001$) (Fig. 2), necrotic components ($p = 0.002$) (Fig. 6), tumor calcification ($p = 0.009$) (Fig. 3), vascular invasion ($p < 0.001$) (Fig. 6), pancreatic duct dilatation ($p < 0.001$) (Fig. 4), and hepatic metastasis ($p < 0.001$) (Fig. 2).

Multiple Logistic Regression Analysis

Multiple logistic regression analysis was performed with stepwise variable selection to produce a multivariate model that included pancreatic duct dilatation, hepatic metastasis, and size of index tumor ≥ 3 cm as significant independent variables associated with the ALT-positive phenotype (Table 3). Despite significance in the univariate analysis, lobulated or irregular shape, necrotic components, tumor calcification, and vascular invasion were not significant in the multiple logistic regression model.

The multivariate combination of pancreatic duct dilatation, hepatic metastasis, and index tumor size ≥ 3 cm was strongly associated with the ALT-positive phenotype (odds ratio = 20.3; 95% CI, 2.3–176.3; $p = 0.006$).

Cox Proportional Hazards Regression Model Analysis

Length of clinical follow-up ranged from 2 months to 12.8 years (mean, 5.4 years; median, 4.7 years). Disease-related mortality was noted in 13 patients (ALT-positive, $n = 10$; ALT-negative, $n = 3$). In the final multivariate model of survival analysis with Cox

TABLE 2: Results of Univariate Analysis

CT Finding	ALT-Positive (*n* = 32)	ALT-Negative (*n* = 89)	*p*
Mean size of index tumor (mm)	53	28	< 0.001[a]
No. (%) of index tumors ≥ 3 cm	24 (75.0)	27 (30.3)	< 0.001[a]
Net enhancement (HU), mean	90.1	101.1[b]	0.252
Lobulated or irregular shape	26 (81.3)	42 (47.2)	0.001[a]
Location			0.402
Pancreatic head or neck	10 (31.3)	36 (40.4)	
Pancreatic body or tail	22 (68.8)	53 (59.6)	
Cystic components	2 (6.3)	14 (15.7)	0.232
Necrotic components	17 (53.1)	21 (23.6)	0.002[a]
Tumor calcification	15 (46.9)	20 (22.4)	0.009[a]
Vascular invasion	14 (43.8)	8 (9.0)	< 0.001[a]
Pancreatic duct dilatation	16 (50.0)	15 (16.9)	< 0.001[a]
Biliary duct dilatation	3 (9.4)	8 (9.0)	1.000
Hepatic metastasis	13 (40.1)	6 (6.7)	< 0.001[a]

Note—Data are number (%) of patients unless indicated otherwise. Quantitative variables (i.e., size of index tumor and net enhancement) were assessed with *t* tests. The remaining qualitative variables were assessed with Fisher exact tests. ALT = alternative lengthening of telomeres phenotype.
[a]Statistically significant difference; $p < 0.05$ was considered as the threshold for statistical significance for all tests.
[b]Data were obtained for 88 patients because of the inability to obtain an accurate ROI measurement for one patient who was therefore excluded.

TABLE 3: Multiple Logistic Regression Analysis Using as Dependent Variable the Presence of Alternative Lengthening of Telomeres (ALT)-Positive Phenotype

CT Feature	No. of Individuals With This Combination of Features	Odds Ratio (95% CI)	*p*
Pancreatic duct dilatation		3.2 (1.2–8.8)	0.02[a]
Hepatic metastases		4.3 (1.3–14.9)	0.02[a]
Size of index tumor ≥ 3 cm		1.4 (1.1–1.7)	0.005[a]
Pancreatic duct dilatation and hepatic metastases	19	12.2 (2.4–62.3)	0.003[a]
Pancreatic duct dilatation and size of index tumor ≥ 3 cm	9	7.0 (2.5–20.1)	0.003[a]
Hepatic metastases and size of index tumor ≥ 3 cm	16	12.8 (3.7–43.7)	< 0.001[a]
Pancreatic duct dilatation, hepatic metastases, and size of index tumor ≥ 3 cm	7	20.3 (2.3–176.3)	0.006[a]

[a]Statistically significant difference; $p < 0.05$ was considered as the threshold for statistical significance for all tests.

proportional hazards regression model, intratumoral calcifications (hazard ratio [HR], 5.2; 95% CI, 1.3–20.4; $p < 0.02$) and hepatic metastases (HR, 9.7; 95% CI, 2.7–34.5; $p < 0.005$) were the only CT features of PanNETs that predicted poor survival irrespective of the ALT status.

Discussion

This study identified several CT features in patients with PanNETs that are associated with the ALT-positive phenotype, which is known to confer a significantly worse prognosis. Tumor size, lobulated or irregular shape, necrosis, intratumoral calcification, vascular invasion, pancreatic duct dilatation, and hepatic metastasis were significantly associated with the ALT-positive phenotype. Irrespective of the ALT status, CT features of PanNETs that predicted poor survival included the presence of intratumoral calcifications and hepatic metastases. ALT-positive PanNETs were larger (mean diameter, 53 mm) than ALT-negative tumors (mean diameter, 28 mm). This difference in size likely reflects the fact that loss of *DAXX* or *ATRX* expression with the associated ALT-positive phenotype is a late event in PanNET oncogenesis and is typically seen in tumors greater than 3 cm [10]. This finding is consistent with previously published data showing an association between tumor size on CT and higher tumor grade at pathology [14–16]. Likewise, CT findings of necrosis and irregular contour have been previously described in association with higher pathologic tumor grade [14], and irregular tumor contour on CT has also been found to predict poor prognosis [17]. CT evidence of tumor calcification has been shown to correlate with tumor grade [18, 19] and the presence of hepatic metastasis [19]. The relatively small number of patients in the subsets of metastatic ALT-positive and ALT-negative phenotypes precluded arriving at a statistically significant difference in survival in this subgroup.

Our findings of vascular invasion, pancreatic duct dilatation, and hepatic metastasis associated with the ALT-positive phenotype suggest invasive, aggressive tumor behavior. Long thought to be indolent tumors (the original term "carcinoid," or "karzinoide" when first described by Oberndofer in 1907 [20] emphasized the nonaggressive "cancerlike" nature of these neoplasms), PanNETs are now recognized to encompass a broad spectrum of tumor behavior ranging from truly indolent to highly aggressive. The association of ALT-positive phenotype PanNETs with hepatic metastasis has been previously described [10, 13] and portends a poor prognosis, conferring an 11% 10-year survival rate [2]. Although previous studies suggest that pancreatic duct dilatation is rare in patients with PanNETs [21, 22], our study found that nearly half of ALT-positive tumors show coincident dilatation of the main pancreatic duct. Additionally, CT evidence of vascular involvement has been described in association with higher tumor grade at pathology [15].

Our multiple logistic regression model showed that pancreatic duct dilatation, tumor size ≥ 3 cm, and the presence of hepatic metastasis are significant individual predictors of the ALT-positive phenotype, with a high predictive value when all three of these findings are coincident. Conversely, the absence of these three findings was strongly predictive of absence of the ALT-positive phenotype. Because multiphasic CT typically precedes surgical resection and definitive pathologic characterization by weeks or months, imaging findings that predict tumor genotype could offer the first insight into prognosis and anticipated tumor behavior, which could be invaluable in driving clinical management. The 2015 National Comprehensive Cancer Network clinical practice guidelines for management of locoregional disease advocate pancreatoduodenectomy or distal pancreatectomy for PanNETs that are > 2 cm or "malignant-appearing"; enucleation, pancreatoduodenectomy, or distal pancreatectomy for PanNETs ≤ 2 cm; and optional observation only for PanNETs ≤ 1 cm [23]. The approach to unresectable or metastatic disease is typically chemotherapy (octreotide or lanreotide chemotherapy with or without everolimus, sunitinib, or cytotoxic chemotherapy) with chemoembolization or ablative therapy, if possible. Although a chemotherapeutic agent specifically targeting the ALT pathway is not yet available, this pathway has been identified as a promising potential pharmacotherapeutic target [24].

The retrospective design of this study with a relatively small population size somewhat limits the predictive value of specific CT characteristics, and our findings should be validated in larger, preferably multiinstitutional, studies. Additionally, although each CT examination included in this study was of adequate diagnostic quality, CT technique was not uniform: 10 studies were performed at outside institutions and the remaining 111 studies performed within our institution were acquired over the course of 10 years, from 2002 to 2012, using multiple scanners. One potential strength of our study is the inclusion of only patients with surgically resected PanNETs, which allowed the complete histopathologic characterization of these tumors, but this may unavoidably bias our study sample toward patients with more aggressive or advanced disease. Finally, although our method of review by consensus has limitations, substantial disagreements were noted in only four cases, all of which involved the degree of vascular involvement.

Using either reviewer's score would not have altered statistical significance.

In conclusion, our study found that PanNETs with the ALT-positive phenotype may be distinguishable from ALT-negative tumors on multiphasic abdominal CT: pancreatic duct dilatation, hepatic metastasis, and tumor size ≥ 3 cm were associated with this aggressive phenotype, which is, in turn, predictive of poor outcome. Our study also showed that intratumoral calcifications and the presence of metastases predicted poor survival independent of the ALT status. Recognition of these characteristics could guide preoperative management and enable clinicians to more accurately assess prognosis.

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